REMARKS

Claims 48-57 and 60-62 were rejected and remain pending. In addition, claims 48, 60, 61, and 62 have been amended herein to recite that the HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele. Applicants' specification fully supports these amendments. For example, Table 5 bridging pages 29 and 30 lists these alleles as being associated with disease. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 48-57 and 60-62.

Specification

The Examiner stated that the sequence listed on page 14 should be notated with sequence identifiers. Applicants respectfully submit that the sequence identifiers in Table 1 of page 14 were added in a response to notice to comply mailed on March 22, 2001. A copy of the March 22, 2001 response can be provided upon request.

Claim objection

The Examiner objected to claim 61 as having a typographical error. Claim 61 has been amended and no longer contains a typographical error. In light of this amendment, Applicants respectfully request withdrawal of the objection to claim 61.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 112, first paragraph, alleging that the specification, while being enabling for the determination of developing severe disease by detecting the presence or absence of some polymorphisms in the HLA-DRB1 allele, does not reasonably provide enablement for the determination of developing severe disease by detecting the presence or absence of any polymorphism in the HLA-DRB1 allele.

Applicants respectfully disagree. A person having ordinary skill in the art reading Applicants' specification would have been able to determine the predisposition of a rheumatoid arthritis patient to develop severe disease as previously claimed. To further prosecution, however, independent claims 48, 60, and 61 have been amended to recite that the HLA-DRB1 allele is an HLA-DRB1 *0401 allele, an HLA-DRB1 *0404 allele, an HLA-DRB1 *0405 allele, or an HLA-DRB1 *0408 allele. As the Examiner acknowledged, the presently claimed invention is fully enabled.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner stated that the phrase "determining the predisposition" in claim 48 is unclear because "there are no endpoints that indicate what qualifies as a patient being predisposed." The Examiner also stated that the term "severe" is a relative term and if this term is known in the art and known to be a particular set of symptoms, then Applicants are requested to point out the known definition of "severe" disease.

Applicants respectfully disagree. The phrase "determining the predisposition" as used in the claims is clear. In fact, a person having ordinary skill in the art reading Applicants' specification would have appreciated that this phrase, as used in the claims, simply means determining whether a rheumatoid arthritis patient is predisposed to develop severe disease in the future. As explained in Applicants' specification, rheumatoid arthritis patients having particular HLA alleles and high frequencies of $CD4^{+}/CD28^{null}$ cells are predisposed to develop severe disease.

Likewise, the term "severe" as used in the claims is clear. According to Applicants' specification, severe rheumatoid arthritis disease can involve major organ involvement, which can be life threatening, and major joint destruction, which can be crippling. See, e.g., page 3,

lines 10-11. Thus, a person having ordinary skill in the art reading Applicants' specification would have understood the meaning of the term "severe" as used in the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. §112, second paragraph.

Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 48-57 and 60-62 under 35 U.S.C. § 103(a) as being unpatentable over Goronzy *et al.* (*J. Clin. Investigation, Inc.*, 94:2068-2076 (1994)) in view of Abril *et al.* (*Arthritis Rheum.*, 40:762 (1998)). Specifically, the Examiner stated that the Goronzy *et al.* reference teaches that most patients with Felty's syndrome and patients with other extra-articular rheumatoid organ manifestations have twice as many disease associated HLA-DRB1 alleles. The Examiner also stated that the Abril *et al.* reference teaches that CD28 deficient $CD4^+$ T cells appear to play a critical role in the disease process leading to RA, suggesting that genes controlling the expression of CD28 deficient T cells represent novel disease risk genes in rheumatoid arthritis. After making these statements, the Examiner concluded that:

> one of ordinary skill in the art would have been motivated to use the teachings of Abril in Goronzy's method of analyzing the presence of $CD4^+$ T cells and clonal expansion of T cells. One would have been motivated by Abril's teaching that CD28 deficient cells represent risk genes in RA. One could have had a reasonable expectation of success that the method and materials of Abril would have worked in Goronzy's method because both are looking at $CD4^+$ T cells' role in RA progression. . . . Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree. Claim 48 recites comparing the frequency of $CD4^+/CD28^{null}$ cells in the patient to a reference frequency to obtain information about the rheumatoid arthritis condition, and determining if the patient is predisposed to develop severe disease based on the information and the presence or absence of a recited HLA-DRB1 allele. The Goronzy *et al.* reference discloses that three of the five patients in the study expressed two

disease-associated HLA-DRB1 alleles, one of which already developed extra-articular manifestations. At no point does the Goronzy *et al.* reference discuss $CD4^+/CD28^{null}$ cell frequencies. The Abril *et al.* reference disclosed that a high frequency of $CD4^+$ $CD28^-$ T cells is correlated with extraarticular manifestations of rheumatoid arthritis. At no point does the Abril *et al.* reference discuss HLA-DRB1 alleles. Moreover, at no point does the combination of references teach or suggest that a person having ordinary skill in the art should assess both $CD4^+/CD28^{null}$ cell frequencies and HLA-DRB1 alleles when determining a rheumatoid arthritis patient's predisposition to develop severe disease. In fact, the combination of cited references fails to provide any indication that $CD4^+/CD28^{null}$ cell frequencies and HLA-DRB1 alleles are independent indicators that should be used together to assess a rheumatoid arthritis patient's predisposition to develop severe disease. This is particularly true given the fact that a person having ordinary skill in the art would have known from Chapman *et al.* (*J. Immunol.*, 157:4771-4780 (1996)) that $CD4^+/CD28^{null}$ cell frequencies are associated with HLA-DRB1 alleles such as HLA-DRB1 *0401. For the Examiner's convenience, a copy of the Chapman *et al.* reference is attached to the accompanying Information Disclosure Statement. Assuming one was motivated to determine a rheumatoid arthritis patient's predisposition to develop severe disease, one might have assessed either $CD4^+/CD28^{null}$ cell frequencies or HLA-DRB1 alleles, but not both. It is Applicants' specification that discloses that $CD4^+/CD28^{null}$ T cell counts are independent of HLA-DRB1 genotype. See, e.g., page 45, lines 11-12.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 48-57 and 60-62 under 35 U.S.C. §103(a).

CONCLUSION

Applicants respectfully submit that claims 48-57, and 60-62 are in condition for allowance, which action is requested. A Petition for Automatic Extension with the required fee is attached. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 9/19/03

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